Aventis Behring

Aventis

30 March 2000

Food and Drug Administration
Center for Biologics Evaluation and Research
Attn: Dockets Management Branch (HFA-305, Room 1061)
5630 Fishers Lane
Rockville, MD 20852

Re: Draft Guidance "Application of Current Statutory Authority to Nucleic Acid Testing of Pooled Plasma" (Docket No. 99D-4577)

We commend the agency on its effort to seek industry comment on implementation of nucleic acid testing intended for use in blood screening and/or manufacturing of blood products. Additionally, we feel that nucleic acid testing may be more sensitive than other methods currently available for early detection of virus during the pre-seroconversion phase of infection and may, therefore, have an added value in blood safety. We request that FDA consider our following four points in response to the draft guidance:

1. The guidance should make adequate distinction between Nucleic Acid Testing (NAT) for in process controls (IPC) versus donor screening. At a recent FDA BPAC meeting (September 16, 1999) viruses, such as parvovirus B19, which currently do not have a licensed serology test for screening blood donors and which produce a self limiting disease, were considered as IPCs and not as donor screening tests (unlike NAT for HBV, HCV, and HIV). It is also Aventis Behring's position that NAT for HAV should be considered an IPC.

2. The guidance should also make adequate distinction between fractionators, manufacturers and plasma collection centers. In the case where the manufacturer is not conducting the NAT donor screening test directly and is receiving plasma that has been previously NAT tested, there is no change to the manufacturing process of the final product. Therefore, in terms of the final product, there should be no requirement for submission of a prior approval supplement (PAS) before distribution of the product.

The FDA, under multiple INDs, has already reviewed the data supporting the validity of NAT. Many products manufactured from plasma screened for a number of viruses by NAT under these INDs are already on the market. The addition of NAT to donor screening will not change the manufacturing process for final products and therefore should have no adverse effect on the identity, strength, quality, purity, or potency of the final product as they may relate to safety or effectiveness.

C 5

99D-4577

Aventis Behring L.L.C.. 1020 First Avenue P.O. Box 61501 King of Prussia, PA 19406-1310
Telephone 610 878 4000

We understand the importance of notifying the FDA that NAT screened plasma is used in the manufacture of final products, but propose that the use of investigational or licensed NAT (referencing the respective IND or BLA) is more appropriate as an annual reportable item.

3. Final product testing (FPT) with NAT and the submission of only CBEs to license applications (CFR314.70 – additional analytical test) does not seem appropriate. This less stringent regulatory requirement may encourage the implementation of a significantly inferior test (see attachment). Products released by FPT NAT may mislead the public into thinking these products are safer than those being screened at the plasma pool level with NAT procedures under an IND as well as allowing manufacturers to make final product label statements.

4. NAT is currently regulated differently between the US, Japan and Europe. We therefore propose that the respective regulatory authorities make an effort to harmonize the requirements on NAT as well as blood/plasma and products manufactured from these components.

Aventis Behring L.L.C. (formerly Centeon L.L.C.) appreciates the opportunity to comment on this draft guidance. If you have any questions regarding this letter please feel free to contact me at (610) 878-4196.

Sincerely,

AVENTIS BEHRING L.L.C.

Jan Fuller Farrar, RAC
Senior Director
Regulatory Affairs

ATTACHMENT

PCR: Final Product Testing vs. Plasma Unit Testing (Donor Screening or IPC)

It is Aventis Behring's position that PCR final product testing as compared to plasma pool screening is a sub-optimal approach to increase the safety of plasma products. Therefore, FDA should ensure through their regulations and approved promotional claims that the respective values of the two tests are taken into consideration.

We have identified four areas pertaining to product safety where final product testing is a less efficient method than plasma pool testing

- Testing at the plasma unit level using pool testing allows the identification of a PCR reactive donation. For viruses such as HBV, HCV and HIV-1, the donor is notified and deferred from donating blood / plasma. Testing at the final product level does not allow such donor screening and therefore maintains PCR reactive donors in the donor pool until they seroconvert. In addition PCR-reactive donors are not sent for medical treatment.
- Testing at the plasma unit level allows significant reduction of the viral load of fractionation pools and all subsequent process intermediates therefore reducing not only the challenge of virus removal and inactivation procedures but also the risk of batch to batch contamination in the manufacturing process.
- We estimate that final product testing is significantly less sensitive than plasma pool testing using today's highest analytical sensitivities (see page 2).
- Finally, PCR reactivity can not differentiate live from inactivated viruses making interpretation of the final container results extremely difficult.

Conversely, we have not identified any area where final product testing would out-perform testing at the plasma unit level. In fact, even with the most sensitive analytical test, final product testing is less sensitive than plasma pool testing.

Respective Sensitivities of Final Product Testing Pertaining to Fractionation Pools and Respective Ability to Reduce Viral Load for Further Processing.

Rationale:

Today's NAT analytical sensitivities (including ultracentrifugation and high volume sample) are in the following ranges regardless of the nature of the sample:

HBV 1 IU/ml
HCV 10 IU/ml
HIV-1 100 GE/ml

Realistic model assumption:

1000 liter fractionation pool
4 log virus removal (only removal is taken into consideration because inactivated virus can still be detected by PCR)
1000 vials of final product (FP)
10 ml per vial
Only one product manufactured from the fractionation pool

1. Final Product Testing

Table 1

	A	B	C	D	E	F
	FP Test sensitivity*	Total / vial	Total / bulk	(Removal [log])	Total / fracti-onation pool	Min. unit concentration which leads to reactive FP
HBV	1 IU/ml	10 IU	10^4 IU	(4)	10^8 IU	$1.25x10^5$ IU/ml
HCV	10 IU/ml	100 IU	10^5 IU	(4)	10^9 IU	$1.25x10^6$ IU/ml
HIV-1	100 GE/ml	1000 GE	10^6 GE	(4)	10^{10} GE	$1.25x10^7$ GE/ml

*maximum achievable, if 16 ml are tested

Read the table as follows (HBV example): Maximum sensitivity for a final container (if 16 ml are tested) is 1 IU/ml (A). In the case of a positive PCR result, a vial would contain a minimum of 10 IU total (1 IU/ml x 10 ml; B). The final bulk, distributed into 1000 vials, would then contain a minimum of 10^4 IU (C). The load in the fractionation pool is calculated by taking into account 4 logs of virus removal (D), resulting in 10^8 IUs (E), which had to be brought in by a unit of 800 ml. The concentration in the unit therefore would be 800 fold less, i.e. $1.25x10^5$ IU/ml (F). This concentration denotes the minimum virus load a plasma unit needed to have to make a final container test PCR positive.

2. Plasma Pool Testing

Table 2

	A Sensitivity / unit level	B Total / pool, if with 5% probability a unit @ DL* enters pool	C (Removal [log])	D Total / bulk	E Total / vial	F Max. virus concentration in FP if B occurred	G Test sensitivity final product**
HBV	10^3 IU/ml	$8x10^5$ IU	(4)	$8x10^1$ IU	0.08	0.008 IU/ml	1 IU/ml
HCV	10^4 IU/ml	$8x10^6$ IU	(4)	$8x10^2$ IU	0.8	0.08 IU/ml	10 IU/ml
HIV-1	10^5 GE/ml	$8x10^7$ GE	(4)	$8x10^3$ GE	8	0.8 GE/ml	100 GE/ml

*DL, detection limit; **maximum achievable, if 16 ml are tested

This table goes the other way around (HBV as example again). If a unit with a virus load at the detection limit (A) would escape detection (5% probability), this unit would contain a maximum virus load of $8x10^5$ IU, which would enter the fractionation pool. Four logs of virus removal would allow 80 IUs to enter the final bulk (D). Distributed into 1000 vials, the resulting virus load per vial would be a maximum of 0.08 IUs (E), the vial concentration (10 ml) would be 0.008 IU/ml (F). This is a minimum of 100-fold (2 log) less than the most sensitive test at the final container level could detect (G).

3. Superiority of Pool Testing for Each "Class" of Plasma Products

The calculations above were done for a model process, where 1 ml of the final product comes out of 100 ml plasma pool. Table 3 provides a simplified overview for some plasma products.

Table 3

	Plasma pool volume used to make 1 ml final product	Factor of higher sensitivity of pool testing *vs.* direct final container testing (assumes 4 log removal by manufacturing process)
Model process	100 ml	2 log
Factor VIII	666 ml	1.2 log
IVIG	40 ml	2.4 log
Albumin	10 ml	3 log

4. Conclusion

Plasma pool testing will result in minute genome concentrations (if at all) in the final product which will virtually be non-measurable, i.e., 1.2 to 3 log below the detection limit of final product testing depending on the nature of the product, Factor VIII or Albumin (see table 3) if we assume a 4 log removal during the manufacturing process. Furthermore, with each log of additional removal factor during the manufacturing process, which has been shown to exist for most of Aventis Behring's products, the difference in sensitivity in favor of pool testing increases further by one order of magnitude.

Document Tracking System -- Office of Blood Research and Review

DCC#: 15795

Applicant: AVENTIS BEHRING L.L.C.

License #:

Product: Nucleic Acid Testing

Type of Appl: LTR Sub Type:

Submission #:

Subject: Draft Guidance

Branch: RPM Branch

RPM: Wilson

Date Out | DH | DTTD | Other | Other Destination

DBA review only

No of volumes: 1

Doc Date: 3/30/00

DCC Recv Date: 3/31/00

Date in DBA: 4/4/00

Sent to RPM: 4/4/00

Date recv RPM

Response that starts clock

Application No Assigned

Date App:

Date Closed:

Notes:

Print this record

Retrieve new record

Routing: To:	MailCode:	Initials:	Date:
Wilson	HFM-380	LW	6 Apr 00
Docket's Mgmt Branch	~~HFM~~ HFA-305		